GLOWORM-PARA: a flexible framework to simulate the population dynamics of the parasitic phase of gastrointestinal nematodes infecting grazing livestock

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ABSTRACT

Gastrointestinal (GI) nematodes are a significant threat to the economic and environmental sustainability of livestock keeping as adequate control becomes increasingly difficult due to the development of anthelmintic resistance (AR) in some systems and climate-driven changes to infection dynamics. To mitigate any negative impacts of climate on GI nematode epidemiology and slow AR development there is a need to develop effective, targeted control strategies that minimise the unnecessary use of anthelmintics and incorporate alternative strategies such as vaccination and evasive grazing. However, the impacts climate and GI nematode epidemiology may have on the optimal control strategy are generally not considered due to lack of available evidence to drive recommendations. Parasite transmission models can support control strategy evaluation to target field trials, thus reducing the resources and lead-time required to develop evidence-based control recommendations incorporating climate stochasticity. GI nematode population dynamics arising from natural infections have been difficult to replicate and model applications have often focussed on the free-living stages. A flexible framework is presented for the parasitic phase of GI nematodes, GLOWORM-PARA, which complements an existing model of the free-living stages, GLOWORM-FL. Longitudinal parasitological data for two species that are of major economic importance in cattle, *Ostertagia ostertagi* and *Cooperia oncophora,* were obtained from seven cattle farms in Belgium for model validation. The framework replicated the observed seasonal dynamics of infection in cattle on these farms and overall, there was no evidence of systematic under- or over-prediction of faecal egg counts (FECs). However, the model under-predicted the FECs observed on one farm with very young calves, highlighting potential areas of

uncertainty that may need further investigation if the model is to be applied to young livestock. The model could be used to drive further research into alternative parasite control strategies such as vaccine development and novel treatment approaches, and to understand GI nematode epidemiology under changing climate and host management.

Keywords: *Ostertagia ostertagi*; *Cooperia oncophora*; Model; Parasite; Population dynamics; Transmission; Nematode; Livestock

1. Introduction

Gastrointestinal (GI) nematodes are increasingly recognised as an important threat to the future sustainability of livestock keeping for food production and leisure. At a policy level, livestock make a significant contribution to agricultural greenhouse gas (GHG) emissions, which may be exacerbated by GI nematode infections (Fox et al., 2018). In 2013, methane emissions from cattle and sheep were responsible for 47% of agricultural GHG emissions in England, and approaching 90% of agricultural GHG emissions in Wales, Scotland and Northern Ireland (Salisbury et al., 2015). GI nematodes also threaten food security and the economic sustainability of livestock farming as they cause significant production losses in ruminants (Nieuwhof and Bishop, 2005; Charlier et al., 2009). For example, a meta-analysis of 88 studies found that lambs infected with GI nematodes experienced a 25% drop in weight gain (Mavrot et al., 2015). Similarly, in cattle, GI nematodes cause significant drops in weight gain and milk yield (Verschave et al., 2014b). Finally, the pathogenic implications of GI nematode infections (e.g. Besier et al., 2016) on host welfare are clear, however the impact of subclinical and chronic infections remains an understudied but important question in livestock helminth research (Morgan et al., 2018).

Currently, the control of GI nematodes in livestock is primarily based on the chemotherapeutic use of anthelmintic substances (Charlier et al., 2014). However, both the influence of climate change and in places the development of AR on farm management and parasite epidemiology are expected to challenge the future control of these infections (Morgan and van Dijk, 2012; Skuce et al., 2013). Progress has been made towards targeted, sustainable control strategies that are economically sound (Charlier et al., 2014) but the need for adequate decision-support tools to aid in the

implementation of these strategies remains (Morgan, 2013). Multiple initiatives promoting the sustainable control of parasites in livestock have been developed worldwide, such as SCOPS (Sustainable Control of Parasites in Sheep; scops.org.uk), COWS (Control of Worms Sustainably; cattleparasites.org.uk), the UK-VET guidelines on parasite control in horses (Rendle et al., 2019) in the UK, and ASKBILL (Kahn et al., 2017) in Australia. These initiatives provide flexibility to adapt their guidelines to different livestock management systems, and, in the case of SCOPS, resource-intensive longitudinal studies evaluating the efficacy of their guidelines in a range of systems are ongoing (e.g. Learmount et al., 2018).

However, the epidemiology of GI nematode infections is a result of complex interactions between parasite, host, climate, farm management and historic control strategies. The efficacy of these guidelines in the diversity of management systems practiced by cattle, sheep, goat and horse keepers worldwide, and their sustainability in the face of climate change and AR cannot be studied empirically without significant resource input and multi-year studies to incorporate inter-annual weather variability and extreme weather events.

Parasite transmission models are useful as they provide the potential to include a variety of processes on different levels and extrapolate current knowledge to alternative scenarios at large temporal scales (Rose et al., 2015). In doing so, model simulations can be used to target resources for empirical research where they are needed most, and guide the development of evidence-based parasite control strategies and tools. The development of mathematical models to simulate the transmission dynamics of GI nematode infections in ruminants dates back several decades. The majority of the existing models were developed specifically for GI

nematode infections in sheep (Verschave et al., 2016a lists 32 models). Fewer models exist for cattle nematodes (Verschave et al., 2016a lists 7 models for *Ostertagia ostertagi*), and model development for equine nematode species dates back only a few years (Leathwick et al., 2015, 2016, 2017). Generic models that provide a framework for GI nematode infections that can be applied to a range of hosts and nematode species are also scarce (Smith, 2011), while their development is of great interest in identifying emergent patterns of change (Molnár et al., 2013; Rose et al., 2014).

Recently, a generic model framework for the free-living phase of GI nematodes that has important modifications on behaviour and development of the larvae on pasture, was developed (GLOWORM-FL, Rose et al., 2015). This model was initially applied to three species of importance in cattle (*O. ostertagi*) and small ruminants (*Haemonchus contortus* and *Teladorsagia circumcincta*), and additional published parameters and data are available to adapt the model to equine cyathostomins (Leathwick et al., 2015), *Cooperia oncophora* in cattle (Sauermann and Leathwick, 2018) and *Marshallagia marshalli* in small ruminants (Carlsson et al., 2013). To fully explore the consequences of different control and management approaches on parasite epidemiology, however, a complementary model for the parasitic phase is needed as host-parasite interactions and host acquired immunity play a crucial part in the transmission dynamics of GI nematodes (Claerebout and Vercruysse, 2000).

The aim of the current study was to develop a conceptual model framework for the parasitic phase of GI nematodes, GLOWORM-PARA, that can be applied to a range of host and parasite species. Here, the model is parameterised and validated for two species that are of major economic importance in cattle, i.e. *O. ostertagi* and *C.*

129 *oncophora.* Previous cattle models have tended to only focus on one nematode
130 species, i.e. *O. ostertagi*, perhaps due to its pathogenic significance compared with *C.*
131 *oncophora*, against which cattle develop an effective immune response. No single-
132 species model exists for *C. oncophora* despite its increasing importance in the context
133 of anthelmintic resistance and treatment failure (Sutherland and Leathwick, 2011).
134 The development of acquired immunity against GI nematodes was modelled and
135 parameterised in a heuristic, but data-driven manner, to provide a transparent and
136 replicable approach. An extensive set of field observations of first season grazing
137 cattle was used for model validation.

2. Materials and methods

2.1 Model framework

The model framework (Figure 1), tracks the mean number of GI nematodes and level of acquired immunity in a group of hosts (i.e. is a population-based mean-field model). State variables and model parameters are defined in Table 1.

Infective third stage larvae, L3, are ingested with herbage (*L3i*) and enter the pool of pre-adult parasitic nematodes (*P*). Pre-adult nematodes either develop to adult nematodes (*A*) or arrest their development as larvae (*Pa*) before developing to the adult stage. Although the model is developed and validated for trichostrongylid nematodes in the present study, it could also be applied to other strongylid species with a broadly similar life cycle (e.g. equine cyathostomins) as all pre-adult stages are modelled as a single state variable and the pre-adult stage involved in arrested development is not specified. This basic representation of the GI nematode life cycle is similar to numerous previous models, as reviewed by Verschave et al. (2016a) and Smith (2011).

$$\frac{\mathrm{dP}}{\mathrm{dt}} = \mathrm{L3i} - \delta\mathrm{P} - \mu_1\mathrm{P} \quad (1)$$

$$\frac{\mathrm{dPa}}{\mathrm{dt}} = -\mathrm{h}_2\mu_2\mathrm{Pa} + \delta\mathrm{h}_1\mathrm{P} \quad (2)$$

$$\frac{\mathrm{dA}}{\mathrm{dt}} = \delta(1-\mathrm{h}_1)\mathrm{P} + \mathrm{h}_2\mathrm{Pa} - \mu_3\mathrm{A} \quad (3)$$

Acquired immunity (*r*) increases in response to exposure to infection (Claerebout and Vercruysse, 2000), in this case L3 ingestion rate (*L3i*), and decays with time, similar to previous models e.g. Roberts and Grenfell (1991). However, the present framework differs from previous models in its representation of *r* as a logistic growth function to

facilitate modelling interactions between host immune response and parasite life-history parameters (Section 2.3.3).

$$\frac{dr}{dt} = \rho(L3i)(1 - r) - \sigma r \quad (4)$$

2.2 Model integration

The model was implemented in R v 3.5.1 "Feather Spray" (R Core Team, 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) using the *lsoda* function of the *deSolve* package v 1.24 (Soetaert et al., 2010) for solving differential equations. The model returns daily output. Anthelmintic treatments (if applicable) are implemented using the *events* argument of the *lsoda* function to reduce the worm burden by a representative percentage for the duration of the residual activity of the product used. For example, an effective moxidectin pour-on treatment for cattle would trigger a reduction in total worm burden of 99% for 35 days. The percentage reduction could be modified, if necessary, to represent vaccination strategies or reduced anthelmintic efficacies observed in the field. Model output is the mean stage-specific worm burden and egg output per host, which can be used to estimate faecal egg count (eggs per gram) if faeces production is known.

2.3 Parameter estimates

Parameterisation of the framework for multiple species is demonstrated using two species infecting cattle that are currently the focus of vaccine development

178 programmes (Matthews et al., 2016): the abomasal nematode *O. ostertagi* and the
179 intestinal nematode *C. oncophora* (Table 2).
180
181 *2.3.1 Seasonally variable parameters*
182 *Arrested development*
183 There is currently no consensus on the mechanisms of arrested (hypobiosis) and
184 subsequent resumed development in trichostrongylid nematodes and numerous
185 confounding factors in available data prevent the development of robust mechanistic
186 models of arrest (Smith, 1974; Michel et al., 1976; Frank et al., 1986; 1988; Eysker,
187 1993; Fernández et al., 1999; Langrova and Jankovska, 2004; Lützelschwab et al., 2005;
188 Langrova et al., 2008). As the numerous potential drivers of arrest are correlated and
189 seasonal (e.g. the age-structure of host populations, host immunity, temperature,
190 moisture and photoperiod), a simplified seasonal approach was taken to estimate
191 seasonal variations in the factor driving arrest rates *(d)* which is used to simulate the
192 proportion of developing pre-adult nematodes that enter a state of arrested
193 development (h_1).
194 For *C. oncophora* and *O. ostertagi* this arrest rate (h_1) was assumed to be related
195 to the development success of eggs and larvae on pasture. *d* was approximated as a
196 7-day moving average, determined by the temperature-dependent development rate
197 (using the *na.ma* function in the *imputeTS* R package v 3.0 (Moritz and Bartz-
198 Beielstein, 2017) and the *ma* function in the *forecast* package v 8.9 (Hyndman and
199 Khandakar, 2008)), whereby the minimum arrest rate is assumed to coincide with the
200 period where development success is at its maximum and the maximum arrest rate is
201 assumed to coincide with the period where development success is at its minimum.

Thus, arrest rate at the current time point, *t,* is a function of the species-specific minimum and maximum arrest rates (h_{min} *and* h_{max}), annual minimum and maximum predicted development success at the study site (d_{min} *and* d_{max}), and predicted development success at the current timestep (d_t).

$$h_1 = h_{(max)} - \left(\frac{h_{(max)} - h_{(min)}}{d_{(max)}}\right) \times d_t \quad (5)$$

The temperature-dependent development rate of eggs and larvae on pasture for *O. ostertagi* was as described in Rose et al., (2015). For *C. oncophora,* development rate data presented in Sauermann and Leathwick (2018) were extracted using Plot Digitizer v2.6.8 (http://plotdigitizer.sourceforge.net/), and a linear model applied to the data using the *lm()* function in R.

The proportion of arrested larvae resuming development (h_2) was assumed to be an inverse function of the driver of arrest (i.e. development success for *O. ostertagi* and *C. oncophora)*:

$$h_2 = \left(\frac{1}{d_{(max)} - d_{(min)}}\right) \times \left(d_t - d_{(min)}\right) \quad (6)$$

L3 ingestion rate and dry matter intake

To calculate the L3 ingestion rate (*L3i*) the average daily dry matter intake (DMI) by grazing cattle was estimated using the equations of MAFF (1975) based on bodyweight (estimated from the bodyweight at turn out using standard age-related growth curves for dairy cattle; Cue et al., 2012, Verschave et al., 2014a). The equations for growing

young stock and adult cows were used for animals with a bodyweight of less than and more than 400kg, respectively. The rate of ingestion of dry matter was estimated as a proportion of the total available herbage consumed (*kgDM*; standing biomass, i.e. kilograms of dry matter per hectare). From this, L3 ingestion rate was estimated as follows (parameter and state variables are defined in Table 1):

$$L3i = -ln\left(1 - \frac{DMI}{kgDM}\right) \times L3h \quad (7)$$

Faeces production and faecal egg counts

Average daily faeces production was estimated based on host bodyweight using the formula of Nennich et al. (2005). Mean faecal egg counts (*FEC*; eggs per gram) for the group of hosts can be estimated from the number of adults (*A*), per adult fecundity rate (λ) and expected daily faeces production (*f*).

$$\mathrm{FEC} = \frac{\mathrm{A}e^{\lambda}}{\mathrm{f}} \quad (8)$$

2.3.2. Constant rates

The development rate (δ) from ingested L3 to mature adult was estimated from a prepatent periods of 17 days for both *O. ostertagi* and *C. oncophora;* (Table 2; Powers et al., 1982).

No data were available in the literature to estimate the mortality rates of arrested larvae due to the confounding effects of resumed development. Therefore, the mortality rate of arrested L4 for both *O. ostertagi* and *C. oncophora* was set at 0.002 after Grenfell et al. (1987). Mortality rates of all other pre-adult and adult nematodes were a function of immunity (section 2.3.3).

244

245 *2.3.3 Immunity and dependent parameters*

246 *Immune response and decay rate*

247 No data were available to formally estimate immunity decay rates (σ) for *O.*
248 *ostertagi* nor *C. oncophora*, therefore three experts in the area of cattle GI nematodes
249 and vaccine development (J. Vercruysse, E. Claerebout (both co-authors in this study)
250 and P. Dorny) were consulted in order to estimate the percentage decay in immunity
251 over a typical housing period. .

252 To estimate the response rate (ρ), it was assumed that protective immunity (r=1)
253 was typically acquired after 1.5 grazing seasons (9 months of exposure punctuated by
254 a 6 month housing period during which immunity is assumed to decay as described
255 above) for *O. ostertagi* and 1 grazing season (6 months) for *C. oncophora* (Armour,
256 1989; Ploeger et al., 1995; Claerebout et al., 1998; Ravinet et al., 2014). Species-
257 specific field observations of L3 density on pasture (*L3h*) over the course of a grazing
258 season were extracted from the raw data from field trials across Europe summarised
259 by Shaw et al. (1998). The data concerned pasture larvae counts from both 'clinical'
260 and 'subclinical' pastures (*i.e.* pastures on which an outbreak of parasitic
261 gastroenteritis in the untreated first season grazers was observed, or not,
262 respectively) and included a mixture of calves that were treated with anthelmintics
263 and untreated controls (Shaw et al., 1998). Using these data, equation 4, the decay
264 rate (σ) and the method described in section 2.3.1 for estimating L3 intake rates, the
265 *optimise* function in R was used to find the response rate that minimised the sum of
266 square error (SSE) for each dataset, given the expectation that r should equal 0.4 and

0.6 after 3 months grazing, and 0.7 and 1 after 6 months grazing for *O. ostertagi* and *C. oncophora,* respectively.

Immunity-mediated regulation of the parasite population

Host acquired immunity is assumed to regulate the parasite population in 3 ways: 1) by exclusion of ingested larvae (increased pre-adult mortality rate), 2) by decreasing the survival of established (adult) nematodes and 3) by decreasing the fecundity of adult nematodes (Barger et al. 1985; Smith and Grenfell 1985; Coyne and Smith 1992; Smith 1994; Stear et al., 1995; Claerebout and Vercruysse, 2000; Garnier et al., 2016). Thus immunity-mediated regulation of the parasite population was incorporated by increasing the mortality rates of pre-adult (μ_1) and adult nematodes (μ_3) and decreasing fecundity (λ) with increasing acquired immunity. As acquired immunity cannot be measured directly (Claerebout and Vercruysse, 2000), little is known about the functional relationship between acquired immunity and these parameters. Therefore, a linear relationship was assumed, whereby mortality increases between the minimum and maximum values, and fecundity decreases between the maximum and minimum values as acquired immunity increases between 0 and 1:

$$\mu_i = \mu_{i(min)} + (\mu_{i(max)} - \mu_{i(min)})r \quad (9)$$

$$\lambda = \lambda_{(max)} - (\lambda_{(max)} - \lambda_{(min)})r \quad (10)$$

2.4 Model validation

289 *2.4.1 Longitudinal data*

290 The model was validated using independent datasets containing longitudinal
291 parasitological data collected during 2012 and 2013, described in detail in Verschave
292 (2015) and summarised in Table S1. The sampled herds consisted of first season
293 grazers located on 7 commercial dairy farms in Flanders (Belgium). The herds were
294 visited monthly from turn out in Spring (April, May or June) until housing in Autumn
295 (September, October or November).

296 Faecal egg counts (FECs) of all animals were performed each month using a
297 modified McMaster technique with a sensitivity of 10 eggs per gram faeces (epg)
298 (MAFF, 1986) and the mean and 95% confidence interval estimated for each month.
299 For this, the *sample* and *replicate* functions in R were used to generate 10,000
300 replicates sampling with replacement. The *quantiles* function was then used with
301 probabilities of 0.025 and 0.975 to obtain the bootstrapped 95% confidence limits for
302 the means of these replicates.

303 For nematode species identification, the positive faecal samples were mixed per
304 herd, cultured and identified according to Borgsteede and Hendriks (1973). Pasture
305 infectivity (density of L3 on herbage; *L3h*) was measured as described in Verschave et
306 al. (2015) each month and every two months respectively in 2012 and 2013 using the
307 modified technique of Taylor (1939).

308

309 *2.4.2 Validation simulations*

310 Mean FECs and 95% confidence intervals reported by Verschave (2015) were
311 corrected for incomplete egg recovery (recovery rate of 55%; Paras et al., 2018). Daily
312 pasture contamination values reported by Verschave (2015) for the entire period of

313 each trial were obtained by interpolation of the monthly pasture contamination
314 values using the *approxfun* function in R. The data collected from each herd formed a
315 separate validation dataset.

316 Daily mean air temperature data used to estimate daily values for development
317 success to estimate arrest rates (equations 5 and 6) were obtained for each herd from
318 the E-OBS gridded dataset (Haylock et al., 2008) based on the location of the village
319 where each herd was located (Table S1) using the *ncdf4* function v 1.17 in R (Pierce,
320 D. 2019. ncdf4: Interface to Unidata netCDF (Version 4 or Earlier) Format Data Files. R
321 package version 1.17. https://CRAN.R-project.org/package=ncdf4).

322 The longitudinal field observations were used to validate species-specific
323 deterministic model simulations. Daily L3 intake rates were estimated from the
324 interpolated field data as described in equation 7. Dry matter intake and faeces
325 production were estimated as described in section 2.3.1. No data were available for
326 standing biomass, therefore, 2000kgDM per hectare was assumed. Although the
327 individuals in the longitudinal datasets were first season grazers (i.e. had never had
328 exposure to *O. ostertagi* nor *C. oncophora*), there is potential for age-related immunity
329 due to the maturation of the immune system (see discussion in Vercruysse and
330 Claerebout, 1997, and Smith et al., 1985). Therefore, host immunity (*r*) was set at an
331 initial value between 0.1 and 0.5 dependent on age at the start of the grazing period
332 (i.e. 6 months of age; r = 0.1, 21 months of age; r = 0.5).

333

334 *2.4.3. Statistical validation: deterministic simulations*

335 Model goodness of fit was assessed using a linear regression through the origin of
336 observed and predicted FECs as described by Rose et al., (2015). The first FEC for each

herd was excluded from statistical validation as this FEC was simply to confirm the absence of infection at turnout. A statistically significant regression with low residual error indicates that the model reproduces the seasonal patterns of the observed FECs. However, statistical significance does not validate the ability of the model to reproduce the magnitude of FECs observed. For this, the slope estimate was used. A perfect linear fit between model predictions and field observations implies an intercept of zero and a slope of 1. A regression through the origin with a slope that is not significantly different from 1, and therefore included in the 95% confidence interval, indicates that the model reproduces the magnitude of observed FECs over the course of the season, with values significantly less than 1 indicating underestimation of FECs and values significantly greater than 1 indicating overestimation of FECs. A high R^2 value indicates that the model captures a significant proportion of the variance in the observed FECs. Due to the relatively small number of individuals in each herd, the potential for considerable individual variation in FECs (Levecke et al., 2011), and the limitations of the McMaster's faecal egg counting method and other flotation techniques (Egwang and Slocombe, 1981), visual comparison of observed and predicted values were incorporated into the evaluation to mitigate against this variability undermining statistical validation.

2.4.4. Qualitative validation: stochastic simulations

Although the framework presented here is a deterministic mean-field model representing a group of hosts, incorporating individual variation is possible and is beneficial for further validation and future evaluation of individual-based parasite control strategies. An additional 50 simulations were run per herd, per nematode

361 species (representing 50 individual hosts) to incorporate the stochastic influences of
362 between-host variation. The aggregation of *L3h* and chance encounters with *L3h*
363 during grazing was incorporated as described in Berk et al., (2016b). The L3 ingestion
364 rate was drawn from a negative binomial distribution using the *rnbinom* function in R,
365 with a mean equal to the observed *L3h* at each time point, and a high level of
366 aggregation, as would be expected for the moderate *L3h* densities observed in this
367 study (k = 1.41; Verschave et al., 2015). For other species or farming systems, the
368 mean and aggregation values could be adapted to reflect the characteristics of the
369 system to be modelled. In addition to stochastic L3 ingestion, between-host variability
370 in immune response was drawn from a negative binomial distribution with a mean
371 equal to ρ and level of aggregation equal to that used for the L3 intake rate, after Stear
372 et al., (2007) suggested that the distribution of the immune response between hosts
373 mirrored that of the parasitological variables.
374 The practical significance of deviations in model predictions from the observed
375 FECs was also considered in the context of the hypothetical use of the simulated FECs
376 to guide further risk assessment (e.g. prompting a FEC or weighing) and potentially
377 trigger anthelmintic treatment in cattle. 50-200 epg is considered a “Medium” to
378 “High” risk egg count (COWS, 2014). Therefore, a deviation of 200 epg in predicted
379 FECs within the range of 0-400 epg could theoretically result in incorrect risk
380 assessment and anthelmintic treatment choices.
381

382 **3. Results**

383 3.1 Parameter estimates

384 Linear regression of the development rates reported by Sauermann and Leathwick
385 (2018) against temperature for *C. oncophora* yielded a statistically significant fit (a = -
386 0.04, b = 0.008, R^2 = 0.8166, $R^2_{adjusted}$ = 0.8058, $F_{(1,17)}$ = 75.7, p = 1.142e-07) with a
387 predicted minimum development threshold of 5℃ (minimum threshold for
388 development = (0-a)/b).

389 Expert opinion placed the estimated decay rate over an average 6 month housing
390 period (Charlier et al., 2010) at between 10% and 50%. Therefore, a 6-month decay
391 rate of 30% was used to estimate a daily decay rate (Table 2).

392 Using optimisation to fit the response rate (ρ) to data from Shaw et al. (1998)
393 yielded a median response rate for *O. ostertagi* of 0.00006 (IQR (inter-quartile range)
394 0.00024) with a median SSE of 0.03205 (IQR 0.32502). For *C. oncophora* this yielded a
395 median response rate of 0.00013 (IQR 0.00040) with a median SSE of 0.00250 (IQR
396 0.11904). The median fitted response rate was used in all subsequent simulations.

397 All other parameter estimates are provided in Table 2.

398

399 3.2 Model validation

400 The R code used for model simulations and validation is provided as supplementary
401 material. The code can be viewed and run in R software, or viewed in a plain text
402 editor.

403 Daily temperature and rainfall data are shown for the location of each herd in
404 Figure S1. The average age at turn out varied between 6 and 21 months (Verschave,
405 2015, Table S1). With the exception of herd 2, longitudinal FEC data used for model

406 validation (Verschave, 2015; Figures 2 and 3; supplementary R code) tended to be low
407 throughout the grazing season. Mean pasture larvae counts (L3h $kgDM^{-1}$) were low at
408 turnout, ranging from 0.001 to 176 L3h $kgDM^{-1}$ (Verschave, 2015; Table S1),
409 potentially accounting for the low FECs. Although the FECs used for validation are
410 typical for calves in their first grazing season with subclinical infections (Shaw et al.,
411 1997).

412 Qualitatively, species-specific simulations for *O. ostertagi* and *C. oncophora*
413 reproduced general observed patterns of FECs over the course of a grazing season in
414 first season grazers (Figures 2 and 3). Overall, the model captured a high proportion
415 of variance in the observed FECs for both *O. ostertagi* (mean R^2 = 0.76) and *C.*
416 *oncophora* (mean R^2 = 0.67) and residual error was low (Table 3). A statistically
417 significant regression through the origin was achieved for 6/7 (*O. ostertagi*) and 3/7
418 (*C. oncophora*) of the validation datasets (Table 3; Figure 4).

419 For *O. ostertagi,* there were both negative and positive deviations in the slope from
420 1 (Table 3) indicating under- or over-prediction of FECs, respectively. However, as the
421 model both under- and over-predicted FECs, there was no evidence of systematic bias.
422 Significant deviations in the slope from 1 were estimated for 3 of the herds (Table 3).
423 Qualitative assessment of model fit against the mean model and 50 individual
424 simulations incorporating individual variation in immune response and the
425 aggregation of L3 on pasture (Figure 2) suggests that these deviations are of no
426 practical significance (section 2.4.4), with the exception of Herd 2, where high FECs
427 were observed at the end of the grazing season while predicted FECs remained low.

428 For *C. oncophora*, there were predominantly negative deviations in the slope from
429 1, indicating underprediction of FEC. A significant deviation in the slope from 1 was

estimated for 5 of the herds (Table 3). Nevertheless, qualitative assessment as above (Figure 3) suggests that these deviations, similar to the *O. ostertagi* simulations, are of little practical significance (section 2.4.4). Herd 2 was, again, an exception, with higher FECs observed than predicted.

4. Discussion

Smith noted, in 2011, that "*Although it was eventually realised that within each class of parasites a single generic model framework with suitably adjusted parameter values could satisfactorily represent almost all the infections of interest… most of the examples of nematode and trematode models in the literature were constructed on an ad hoc basis to address issues dealing with control of a specific parasite in a specific host in a specific country*". Although many of the models published in recent decades contain important differences in the focus of detail necessary for the specific application of the model (e.g. Laurenson et al., 2011; Cornell et al., 2004), more widely applicable models use proprietary software (e.g. Learmount et al., 2006) or are developed using complex spreadsheets (e.g. Sauermann and Leathwick 2018) that can be difficult to reproduce. Furthermore, differences in the structure of the various model frameworks available and their parameters prevent direct comparisons between model outputs.

Here, GLOWORM-PARA, a generic model framework for the parasitic phase of GI nematode infections is presented. The model can be adapted to different host and nematode species and was developed to complement a previously published model of the free-living stages (GLOWORM-FL; Rose et al., 2015). The model's flexibility is demonstrated by parameterisation for two economically important trichostrongylid species infecting cattle worldwide, *C. oncophora* and *O. ostertagi,* and validation against multiple independent datasets. To our knowledge, no previous attempt has been made to model *C. oncophora* transmission alone.

Aspects of the framework that can be adapted to represent the host-parasite system of interest, are highlighted throughout. For example, parameter *d*, the factor

459 driving arrested development, could be adapted to include immunity (e.g. to simulate
460 the periparturient rise in faecal egg counts in ewes), or to extend the estimate of
461 development success (used here for *C. oncophora* and *O. ostertagi*) to include the
462 impacts of desiccation to simulate seasonal arrest in arid regions. In addition, reduced
463 weight gain and parasite-induced anorexia is an economically important impact of GI
464 nematode infection that has been the focus of many previous models (e.g. Berk et al.,
465 2016a; Laurenson et al., 2011) but was not considered here.

466 Reduced weight gain could be included in the model by substituting the Cue et al.
467 (2012) equation used here with one that estimates weight gain based on worm burden,
468 and also estimating dry matter intake as a function of worm burden to simulate
469 parasite-induced anorexia (e.g. Berk et al., 2016a). The simulations presented here also
470 assumed constant herbage biomass throughout the grazing season due to the lack of
471 data and models to track grass growth. Incorporating models of grass growth, and thus
472 seasonal changes in biomass, may improve predictions by acting on the L3 ingestion
473 rate (i.e. rate of infection, which is a function of dry matter intake rates, total L3 on
474 herbage and available standing biomass). Berk et al. (2016b) incorporated mean
475 monthly grass growth rates for England in their model of *O. ostertagi* in calves.
476 However, this, and infection-dependent host growth, was beyond the scope of the
477 current study, which was to develop a minimal, location-independent framework that
478 could be easily parameterised for multiple species and host systems.

479 GLOWORM-PARA is a mean-field model, simulating the mean trajectory of parasite
480 population dynamics and host immunity in a group of hosts. Mean-field models are
481 useful to explore changes in the system under disparate conditions, such as under
482 current climate and predicted climate change (Rose et al., 2016), and to evaluate the

483 impact of competing management strategies at a herd/flock level (Learmount et al.,
484 2012). However, in an attempt to stem the development of AR, the focus of parasite
485 control has turned from whole-group treatments to targeted selective treatment
486 (TST), where individuals in a flock/herd are treated either based on parasitological
487 indicators (e.g. FECs in horses and sheep; Matthews and Lester, 2015; Kenyon and
488 Jackson, 2012) or based on performance indicators (e.g. liveweight gain in sheep and
489 cattle; Kenyon and Jackson, 2012). The framework can be adapted to incorporate
490 environmental stochasticity, as demonstrated here, to simulate the heterogeneity of
491 intensity of infection between hosts that forms the basis of selection for TST. This was
492 demonstrated by incorporating stochastic L3 intake rate and immune response in the
493 present study.

494 Limitations of previously published detailed mechanistic approaches include an
495 incomplete understanding of the processes and pathways involved in host immunity
496 to GI nematode infection (although this is disputed by some; Roberts, 1999) and the
497 detailed and invasive immunological datasets required to parameterise these models.
498 The latter is a severe impediment to applying these models to understudied systems
499 and necessitates a more simplified approach to modelling acquired immunity
500 regardless of whether or not there is an adequate understanding of the underlying
501 processes. Complete representation of relevant immunological pathways, supported
502 by sufficient empirical data to estimate parameters, is therefore difficult to achieve
503 for most GI nematode species and is acknowledged as a bottleneck in the production
504 of mathematical models for the population dynamics of GI nematodes (Charlier et al.,
505 2018).

506 Previous models of GI nematode population dynamics and transmission have
507 differed in their approach to modelling acquired immunity, which increases during the
508 course of an infection (Claerebout and Vercruysse, 2000). For example, some model
509 acquired immunity as a simple increasing function of the time of exposure to infection
510 (Berk et al., 2016a; Learmount et al., 2006), exposure to larvae (Grenfell et al., 1995),
511 host age (Garnier et al., 2016), or worm burden (Cornell et al., 2004), or
512 mechanistically via the impact of exposure to infection on immunological parameters
513 (Singleton et al., 2011; Prada Jiménez de Cisneros et al., 2014). Practical limitations of
514 the former examples include the absence of upper boundaries on the levels of
515 acquired immunity, which subsequently introduces difficulties scaling immune-
516 mediated parasite life-history parameters. Practical limitations of the latter examples
517 involve the need for invasive immunological measurements (plasma IgA) to estimate
518 immune response rates.
519 The model presented here represents immunity as a logistic growth function. This
520 allows an exponential response with cumulative exposure to GI nematodes, mimicking
521 the stronger immune response that would be expected after administration of a
522 challenge infection or a booster vaccination, and limits acquired immunity to values
523 less than 1 to facilitate modelling interactions between host immune response and
524 parasite life-history parameters. This simple approach also facilitates model
525 application in data-sparse systems. To effectively model the development of host
526 acquired immunity to GI nematodes without explicit representation of the
527 complexities of the immune response and the necessary data for parameterisation,
528 the decay and response rates for the logistic function are estimated using a
529 combination of empirical, non-invasive field data, qualitative observational data and

530 expert judgement. This approach requires fewer data for parameterisation than a
531 more detailed mechanistic representation of immunity, and therefore permits
532 application of this framework to a wider range of host-parasite systems than would
533 be possible with a more detailed model. Nevertheless, there is scope to adapt the
534 representation of immunity as more data become available. It would also be possible,
535 with slight adaptation of the model, to apply varying levels of host immunity to the
536 different within-host life cycle stages, for example to simulate the use of vaccines with
537 parasite stage-specific activity.

538 Overall, the mean-field model captured a high proportion of the variability in the
539 observed FECs (*O. ostertagi* mean $R^2 = 0.76$ and *C. oncophora* mean $R^2 = 0.67$). Residual
540 error can be attributed to multiple sources, including measurement error in the
541 pasture larvae counts used to initiate the model simulations (Couvillion, 1993),
542 multiple sources of variability in the FEC method used in the validation dataset
543 (Levecke et al., 2015), and individual host variability as described above. There was no
544 evidence of systematic bias for *O. ostertagi*, and although the *C. oncophora* model
545 tended to underestimate FECs, the difference in observed and predicted FEC were of
546 no practical significance (section 2.4.4; COWS, 2014). The statistical significance of
547 small deviations in predicted FEC from observed FEC (<25 eggs per gram in herds 1, 2,
548 and 4; Figure 3) highlights the importance of pragmatic validation methods including
549 statistical, negative binomial models and qualitative appraisal. This is again
550 highlighted by herd 7 which performed poorly in the statistical validation, despite low
551 residual error and high R^2 values (Table 3), and the predicted FECs being within a
552 reasonable range of the observed FECs for both species tested. This was likely due to
553 failure of the model to capture a slight, practically insignificant, increase in FEC for

554 both species mid-August. Despite the overall good performance of the model, there
555 were some exceptions. Herd 1 produced a high *C. oncophora* FEC one month after
556 turnout, that was not predicted by the model and could be of practical significance, as
557 FECs of the level observed would usually require treatment. The FECs observed for
558 herd 2 were significantly higher than predicted for both species, with differences at
559 the end of the grazing season in the order of several hundred eggs per gram. One
560 plausible hypothesis for this, given the good performance of the model for most other
561 herds, is that the individuals on this farm were particularly susceptible to GI nematode
562 infection, which could be due to a number of factors such as genetics, nutrition and
563 coinfection (which cannot be interrogated within the current dataset). Alternatively,
564 the underprediction of FEC on this farm may indicate model bias when applied to
565 young cattle – the calves simulated in Herd 2 were the youngest of all the farms used
566 for model validation (6 months, cf. 10-21 months). Further validation would be
567 required before applying the model to simulate very young calves (<10 months of
568 age), to determine if this discrepancy is due to the susceptibility of the calves on this
569 farm (posited above), an overestimate of immune response in younger calves, or a
570 non-linear relationship between acquired immunity and the parasitological
571 parameters.

572 To conclude, a generic framework to simulate the parasitic phase of GI nematode
573 infections is presented here and its flexibility is demonstrated by simulating *O.*
574 *ostertagi* and *C. oncophora* infections. The model simulations replicated infection
575 patterns of first season grazers for these nematode species. The lead authors have
576 previously developed a complementary framework for the free-living stages of the GI
577 nematode life cycle, which has been applied to several GI nematode species, and has

578 also been successfully adapted to simulate the development and dispersal of cattle
579 lungworm (*Dictyocaulus viviparus;* McCarthy, 2018). It is hoped that GLOWORM-PARA
580 will drive similar innovation and international collaboration by providing an accessible
581 and transparent framework that can be adapted to multiple species and extended
582 where additional detail is required. Future research will integrate GLOWORM-PARA
583 with GLOWORM-FL and host-parasite interactions (host movements, anthelmintic
584 treatments etc.) to obtain a full lifecycle framework for the evaluation of alternative
585 GI nematode control strategies.

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Declaration of interest

None to declare.

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Figure 1. Conceptual framework of the GLOWORM-PARA model. State variable and parameter definitions are given in Table 1. Solid arrows indicate life-cycle transitions (e.g. from ingested L3 (L3i) to pre-adult (P) to adult (A)), mortality (μi) or deposition of eggs (λ). Dashed arrows indicate dependencies (e.g. the level of acquired immunity (r) depends on the intake of L3 (L3i)).

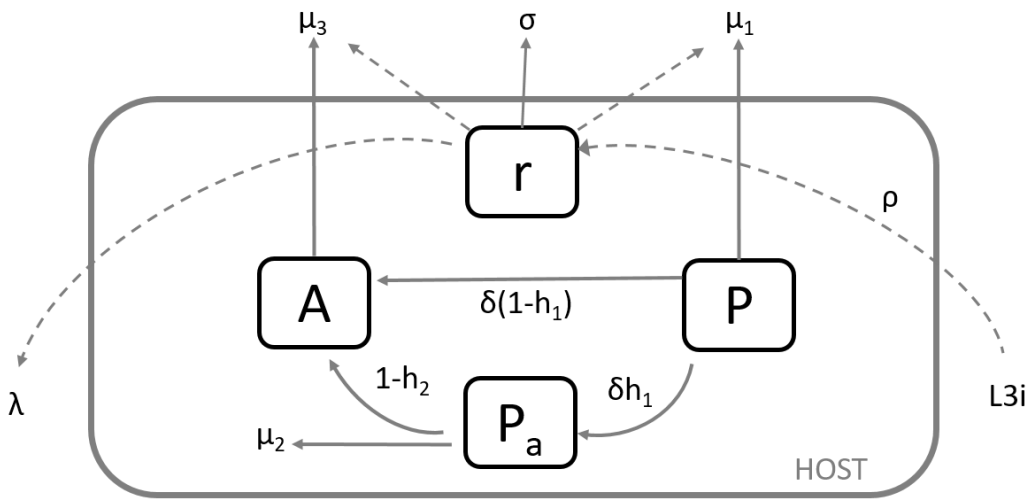
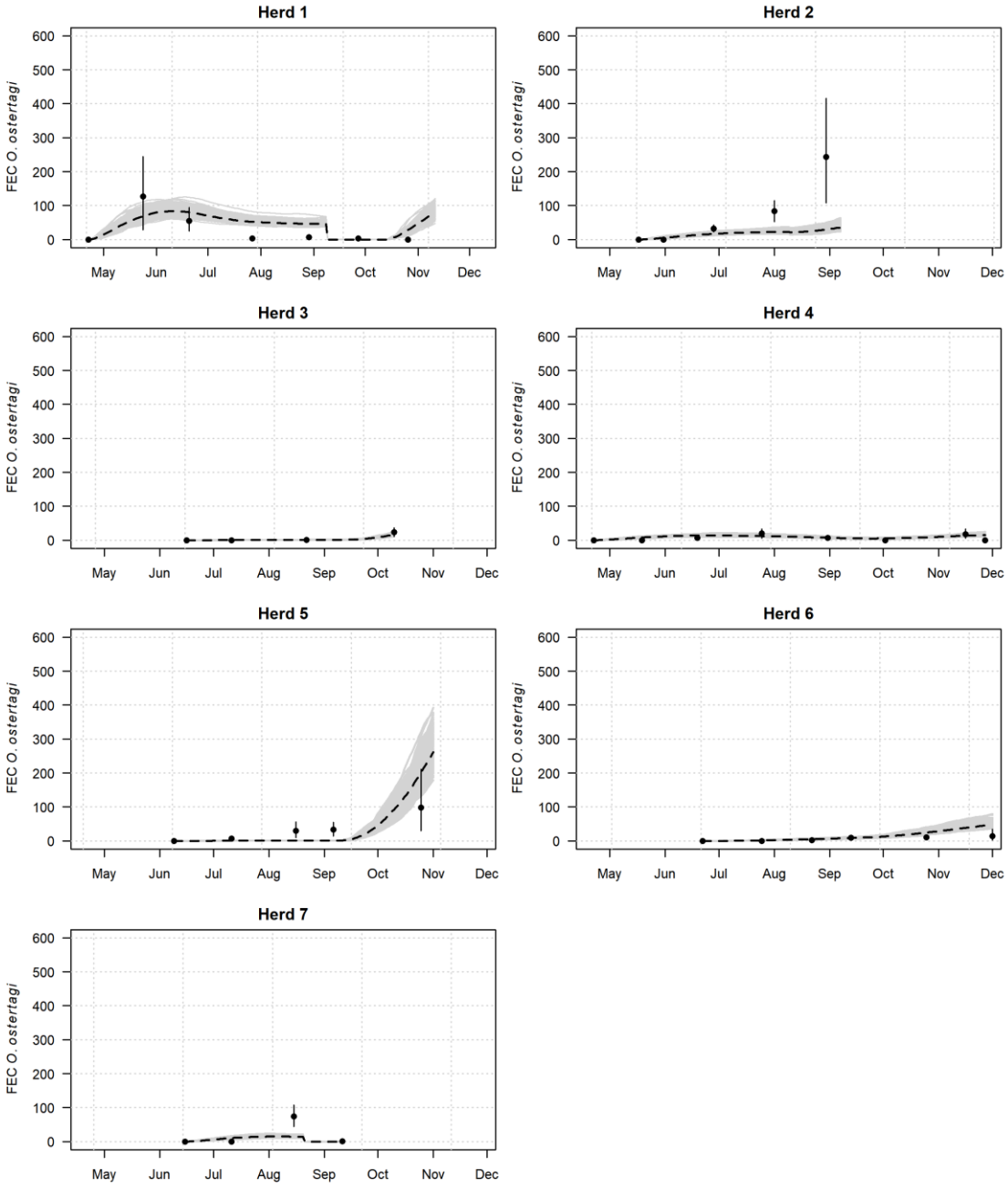


Figure 2. Observed and predicted faecal egg counts (FEC) for *O. ostertagi* in first season grazing animals of dairy herds in Belgium. Animals were followed for the entire length of the first grazing season, further information on the background of this data can be found in Supplementary Table S1. Points and error bars show the observed number of eggs per gram faeces (epg) and the corresponding 95% confidence interval obtained by bootstrapping (10,000 repeats). The dashed black line depicts the predicted FEC for a group of hosts. The solid grey lines depict predictions obtained from 50 model simulations representing individual hosts, in which stochastic L3 intake and between-host variability in immune response were incorporated.



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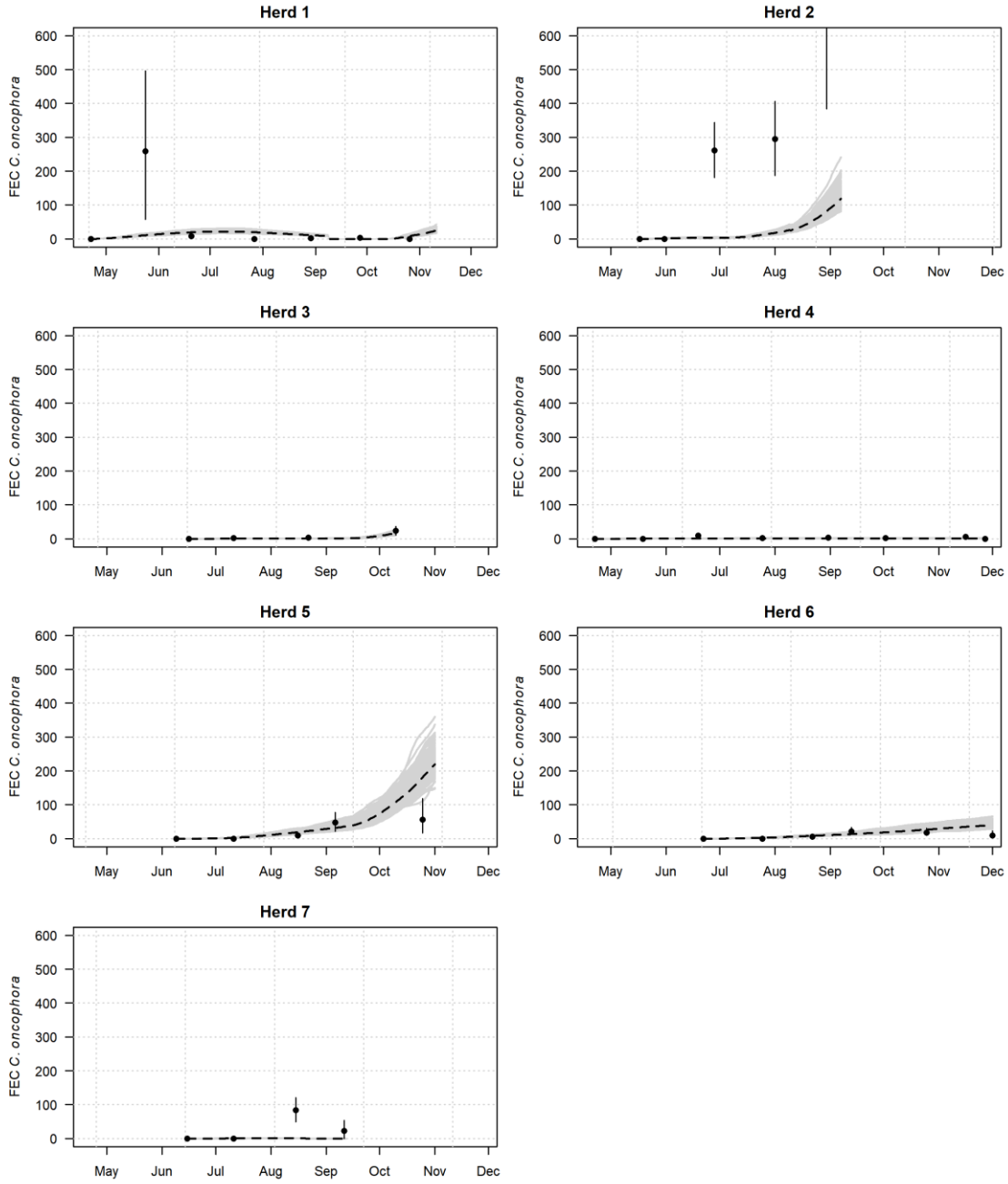
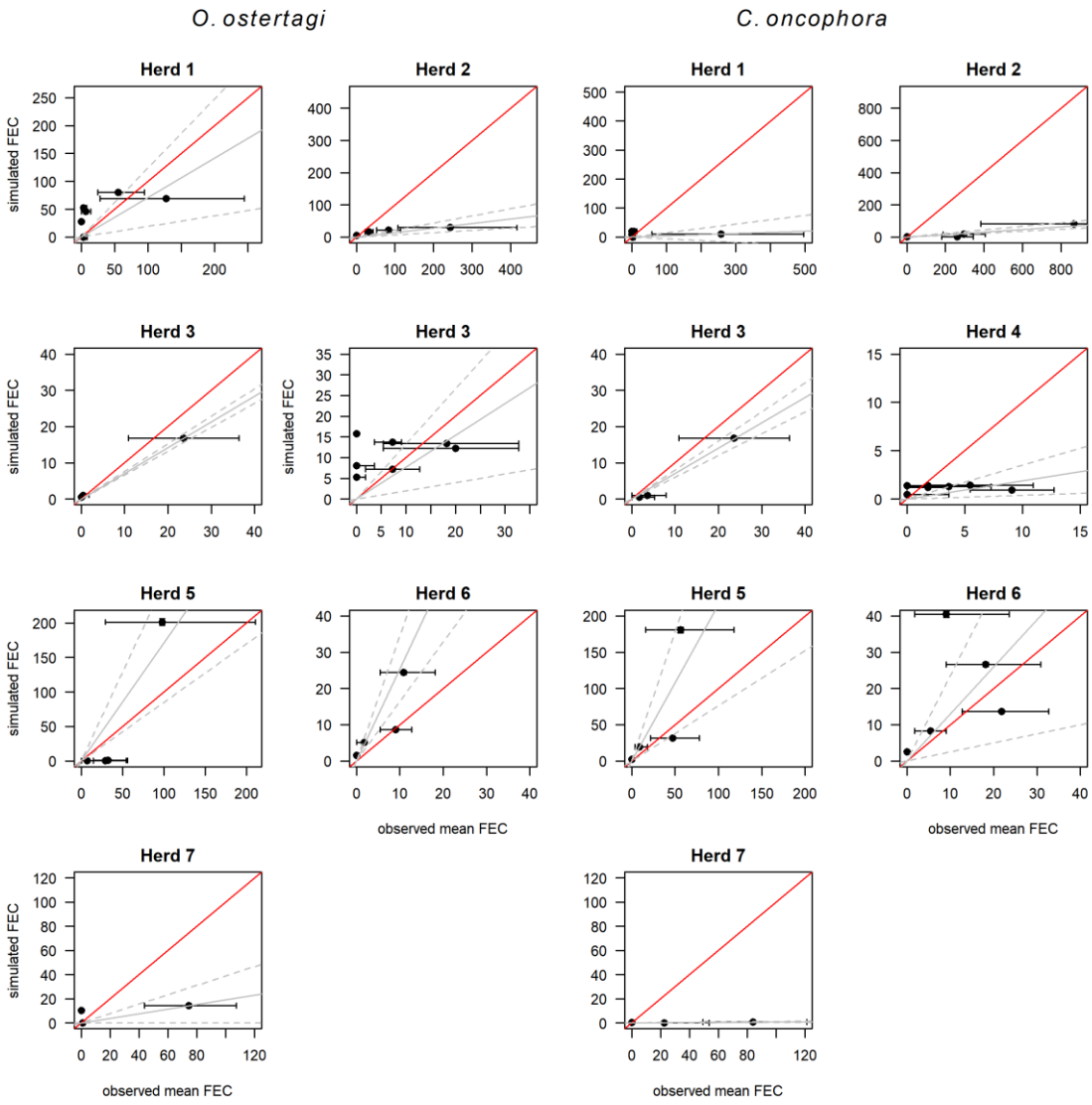
899 Figure 3. Observed and predicted faecal egg counts (FEC) for *C. oncophora* in first
900 season grazing animals of dairy herds in Belgium. Animals were followed for the entire
901 length of the first grazing season, further information on the background of this data
902 can be found in Supplementary Table S1. Points and error bars show the observed
903 number of eggs per gram faeces (epg) and the corresponding 95% confidence interval

obtained by bootstrapping (10,000 repeats). The dashed black line depicts the predicted FEC for a group of hosts. The solid grey lines depict predictions obtained from 50 model simulations representing individual hosts, in which stochastic L3 intake and between-host variability in immune response were incorporated.



910 Figure 4. The observed and simulated FECs (points) with 95% confidence intervals
911 (observed = horizontal, simulated = vertical). The red line indicates hypothetical
912 perfect agreement between the observed and simulated FECs. The grey solid line
913 indicates the predicted slope of the regression, with 95% confidence intervals show
914 as grey dashed lines. Note that the 95% confidence intervals for the simulated data
915 (estimated using the stochastic simulations shown in grey in figures 2 and 3) are
916 narrow and may not be easily seen due to the scale of the y-axes.


O. ostertagi
C. oncophora
Herd 1
Herd 2
Herd 3
Herd 4
Herd 5
Herd 6
Herd 7
simulated FEC
observed mean FEC

917

918

Table 1. State variable and parameter definitions

State variable / Parameter	Definition	Units
P	Pre-adult nematodes in the host (L3, L4 and immature adults)	-
Pa	Arrested L4	-
A	Mature adults	-
r	Acquired immunity	-
$L3h$	L3 density on herbage	L3 kg dry matter^{-1}
$L3i$	L3 ingestion rate	L3 day^{-1} host^{-1}
δ	Development rate from ingested L3 to mature adult	P^{-1} day^{-1}
μ_1	Pre-adult mortality rate	P^{-1} day^{-1}
μ_2	Arrested L4 mortality rate	Pa^{-1} day^{-1}
μ_3	Adult mortality rate	A^{-1} day^{-1}
h_1	Rate of developing pre-adult nematodes entering arrested development	P^{-1} day^{-1}
h_2	Rate of arrested larvae resuming development	Pa^{-1} day^{-1}
ρ	Immune response	L3i^{-1}
σ	Immune decay	Day^{-1}
λ	Daily fecundity (eggs produced)	Eggs worm^{-1} day^{-1}
f	Daily faeces production	Grams (wet weight) day^{-1}
d	Driver of arrest	N/A[a]
DMI	Daily herbage dry matter intake	Grams day^{-1}
$kgDM$	Standing biomass (herbage) on pasture	kg dry matter hectare^{-1}
FEC	Faecal egg count	Eggs gram^{-1}

[a] As this parameter is used to scale the immune-dependent parameters, the unit needs not be fixed. In the present study, the temperature-dependent development rate of *O. ostertagi* and *C. oncophora* has been used as an indicator of development success. However, other, more complex indicators can be used where sufficient data exist for parameterisation, such as Q0 estimates or the proportion of eggs surviving to L3 on pasture, or this parameter can be adapted to incorporate immunity-driven arrested development.

927 **Table 2.** Parameter estimates for *Ostertagia ostertagi* (Oo) and *Cooperia oncophora*

928 (Co).

Parameter	***Species***	***Estimate***	***Source***
$\boldsymbol{\delta}$	*Oo. Co*	-ln(0.5)/17= 0.041	Powers et al., (1982)
$\boldsymbol{\mu_{1(min)}}$	*Oo*	0.054	Mean in Verschave et al. (2014a)
	Co	0.044	Mean in Verschave et al. (2016b)
$\boldsymbol{\mu_{1(max)}}$	*Oo*	0.062	Upper 95% CI in Verschave et al. (2014a)
	Co	0.052	Upper 95% CI in Verschave et al., (2016b)
$\boldsymbol{\mu_2}$	*Oo, Co*	0.002	Grenfell et al. (1987)
$\boldsymbol{\mu_{3(min)}}$	*Oo*	0.028	Mean in Verschave et al. (2014a)
	Co	0.039	Mean in Verschave et al. (2016b)
$\boldsymbol{\mu_{3(max)}}$	*Oo*	0.032	Upper 95% CI in Verschave et al. (2014a)
	Co	0.048	Upper 95% CI in Verschave et al., (2016b)
$\boldsymbol{h_{(min)}}$	*Oo*	0.02	Lower 95% CI in Verschave et al. (2014a)
	Co	0.004	Lower 95% CI in Verschave et al., (2016b)
$\boldsymbol{h_{(max)}}$	*Oo*	0.06	Upper 95% CI in Verschave et al. (2014a)
	Co	0.011	Upper 95% CI in Verschave et al. (2016b)
$\boldsymbol{\rho}$	*Oo*	5.981×10^{-5}	Current study (fitted to data from Shaw et al. (1998), see main text for assumptions)
	Co	1.316×10^{-4}	Current study (fitted to data from Shaw et al. (1998) , see main text for assumptions)
$\boldsymbol{\sigma}$	*Oo, Co*	-ln(0.7)/(6*30) = 0.002	Current study (expert opinion)

$\boldsymbol{\lambda_{(min)}}$	*Oo*	ln(196/2) = 4.58	Lower 95% CI in Verschave et al. (2014a)
	Co	ln(1253/2) = 6.44	Lower 95% CI in Verschave et al. (2016b)
$\boldsymbol{\lambda_{(max)}}$	*Oo*	ln(284/2) = 4.96	Mean in Verschave et al. (2014a); assuming a 1:1 sex ratio
	Co	ln(2968/2) = 7.30	Mean in Verschave et al. (2016b); assuming a 1:1 sex ratio
d	*Oo*	−0.07258 + 0.00976T[a]	Rose et al. (2015)
	Co	−0.0401 + 0.00821T[a]	Current study (fitted to data from Sauermann and Leathwick (2018))

929 [a]T = daily mean air temperature (°C)

930

Table 3. Validation of simulations for faecal egg counts (FEC) of *O. ostertagi* and *C. oncophora* using parasitological data of first season grazing animals on seven commercial dairy herds in Belgium.

	Ostertagia ostertagi				***Cooperia oncophora***			
Dataset	Error (residual sum of squares)	Linear regression	R^2 ($R^2_{adjusted}$)	Slope (95% CI)	Error (residual sum of squares)	Linear regression	R^2 ($R^2_{adjusted}$)	Slope (95% CI)
Herd 1	37.69	$F_{1,5}$ =6.89, p=0.047	0.58 (0.50)	0.71 (0.19 – 1.24)	13.75	$F_{1,5}$ =0.69, p=0.445	0.12 (-0.06)	0.04 (-0.06 – 0.15)
Herd 2	10.11	$F_{1,3}$ =13.35, p=0.035	0.82 (0.76)	0.14 (0.07 – 0.22)	12.62	$F_{1,3}$ =41.06, p=0.008	0.93 (0.91)	0.08 (0.06 – 0.11)
Herd 3	0.61	$F_{1,2}$ =766.7, p=0.001	1 (1)	0.71 (0.66 – 0.76)	1.21	$F_{1,2}$ =191.3, p=0.005	0.99 (0.98)	0.70 (0.60 – 0.80)
Herd 4	8.38	$F_{1,6}$ =7.00, p=0.038	0.54 (0.46)	0.77 (0.20 – 1.33)	0.92	$F_{1,6}$ =5.90, p=0.051	0.50 (0.41)	0.19 (0.04 – 0.35)
Herd 5	47.31	$F_{1,3}$ =15.1, p=0.030	0.83 (0.78)	1.71 (0.85 – 2.57)	53.02	$F_{1,3}$ =9.12, p=0.057	0.75 (0.67)	2.16 (0.76– 3.56)
Herd 6	9.42	$F_{1,4}$ =30.35, p=0.005	0.88 (0.85)	2.54 (1.64 – 3.45)	16.25	$F_{1,4}$ =5.9, p=0.07	0.60 (0.50)	1.30 (0.25–2.35)
Herd 7	7.39	$F_{1,2}$ =3.84, p=0.189	0.66 (0.49)	0.19 (-0.0002 – 0.39)	0.24	$F_{1,2}$=6.48, p=0.126	0.76 (0.65)	0.007 (0.002 – 0.013)

935 **Supplementary Table S1.** Characteristics of the first season grazing stock and the grazing season used for the collection of longitudinal parasitological data
936 (Verschave 2015). These data were used for model validation. Approximate stocking rates are shown where the values are known.

	Herd 1	**Herd 2**	**Herd 3**	**Herd 4**	**Herd 5**	**Herd 6**	**Herd 7**
Location	Dudzele	Malle	Evergem	Oudenaarde	Drongen	Sinaai	Eeklo
Number of animals at turn out	11	12	10	19	11	16	16
Average age at turn out (months)	20	6	21	19	11	15	10
Average body weight (kg)	487	99	439	505	361	375	264
Date of turn out	20/04/2012	15/05/2012	14/06/2013	20/04/2013	07/06/2013	20/06/2013	13/06/2013
Date of stabling	09/11/2012 *	06/09/2012	20/09/2013 *	26/11/2013 *	14/10/2013	30/11/2013	10/09/2013
Stocking rate (animals per hectare)	-	-	5.2*	13*	62.4	3.7	25.5
Anthelmintic treatment performed	Yes	Yes	No	No	No	No	Yes
Date of anthelmintic treatment	7/9/2012	7/9/2012	-	-	-	-	19/08/2013
Anthelmintic substance	Moxidectin, pour-on formulation	Doramectin, injectable formulation	-	-	-	-	Moxidectin, pour-on formulation
Mean L3 kgDM^{-1} at turnout	176	35	1	18	1	0.001	45

937 * Several animals of these herds were stabled earlier due to impending partus.
938

Supplementary Figure S1. Mean daily temperature (left column) and total daily rainfall (right column) for the observation period for each herd observed by Verschave (2015). Data were obtained from the E-OBS gridded dataset (Haylock et al., 2008) based on the village where each herd was located (Table S1).